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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/974,703	10/10/2001	Douglas E. Vaughan	1242/39/2	7969

25297 7590 11/28/2003

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EXAMINER	
PATTEN, PATRICIA A	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,703	VAUGHAN, DOUGLAS E.	
	Examiner	Art Unit	
	Patricia A Patten	1654	

-- Th MAILING DATE of this communication appears on the cov r sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *18-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s).~~ 7/23/2002
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-36 are pending in the application.

Election/Restrictions

Applicant's election of Group I, claims 1-17 in the response filed 10/31/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 18-36 are hereby withdrawn from the merits as being drawn to a non-elected invention.

Claims 1-17 were examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing risk of cardiovascular disease, does not

reasonably provide enablement for prevention of such disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inventions targeted for prevention bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The term 'prevention' is deemed to be a 'cure' since prevention of a disease is interpreted to mean that the disease will entirely cease to manifest after administration of the carcinogen. The standard of enablement is higher for such inventions because as the state of the art stands, there is no 'prevention' or 'cure' for cardiovascular diseases. Thus, claims to prevention of cardiovascular disease may be unbelievable in the absence of strong supporting evidence.

There is no conclusive evidence in the Instant disclosure which indicates that the ACE inhibitors completely hindered cardiovascular disease in a patient. Although inhibition of ACE appears to stunt the endogenous production of thrombosis factors due to the inhibition of PAI-1, cardiac malfunction may manifest from numerous other underlying conditions such as hypertension and genetic valve defects for examples.

The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the skilled artisan with specific treatment regimens that achieve complete prevention. The specification does not provide this guidance. Without such guidance in the specification and the lack of correlative working examples, the claims would ***require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan***.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; ***however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112***; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved." (emphasis added)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 10 recite 'healthy subject'. The metes and bounds of the term 'healthy' are not clearly delineated. Although claims 3 and 12 narrow the phrase 'healthy subject' to subjects which do not suffer from certain diseases, the recitation of 'healthy subject' in claims 1 and 10 is indefinite for the following reason: The term 'healthy' is vague. A person having thyroid disease may be 'healthy' if they take care of themselves and/or take medication as prescribed. Alternatively, a person who has had myocardial infarction, after taking care of themselves and taking medication may return to a 'healthy' state. Because the Examiner cannot ascertain the intended boundaries of the phrase 'healthy subject', claims 1 and 10, as well as subsequent claims which depend upon claims 1 and 10 but do not define this phrase by limiting the phrase (as in claims 3 and 12), will be examined on the merits as if it were limited to the particulars of claims 3 and 12 respectively.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (1998) or Uehara et al. (1998). Claim 1 is drawn to a method for significantly reducing a risk of cardiovascular disease via administration of an ACE inhibitor.

Brown et al. (1998) taught that ACE inhibition of the RAS (renin-angiotension system) decreased progression of atherosclerosis in animal models and reduced the risk of recurrent MI in patients with left ventricular dysfunction (p.965). Brown et al. performed ACE inhibition tests with quinapril on subjects which were free from cardiovascular diseases (p.966-Methods). Analysis concluded that administration of quinapril "...significantly lowers PAI-1 antigen and activity..." (p.969, Discussion and Figure 4).

Uehara et al. (1998) studied ACE inhibition on PAI-1 (plasminogen activator inhibitor) in diabetic rats (p. 327-Abstract). Upon evaluating the data produced from administration of imidapril and enalapril to diabetic rats, Uehara et al. stated that "The concentrations of PAI-1 in plasma were significantly increased in the untreated OLETF rats compared with those in the control LET rats" (p.331 and Figure 5, p. 333).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (12/1998) in view of Vaughan (1997).

The teachings of Brown et al. were discussed *supra*. Brown et al. clearly stated that it was well known in the art that PRA had been associated with risk of myocardial infarction, and ACE inhibitors reduced the risk of recurrent myocardial infarction in patients with left ventricular dysfunction (p.965). Brown et al. did not specifically teach wherein the ACE inhibitor was ramipril, wherein the ACE inhibitor was administered to a person having a PAI-1 polymorphism which resulted in elevated PAI-1 or wherein the method reduced PAI-1 by at least about 35% compared to baseline.

Vaughan (1997) displayed the biochemical mechanism associated with Angiotensin, PAI-1 and Bradykinin in Figure 3. Vaughan explained that "Inhibition of the conversion of angiotensin to smaller peptides by an ACE inhibitor or by an aminopeptidase inhibitor prevents the expression of PAI-1" (p.14). Vaughan clearly

taught that increased blood PAI-1 levels was a key in thrombus development which led to cardiovascular complications (p.13).

One of ordinary skill in the art would have been motivated to have administered an ACE inhibitor to a person having a PAI-1 polymorphism, wherein said polymorphism produces excess levels of PAI-1 because PAI-1 is a primary cause of thrombosis which can lead to cardiovascular disease as taught by Vaughan. It was clear from Vaughan that ACE inhibition subsequently inhibited PAI-1 production. Therefore, the ordinary artisan would have had a reasonable expectation that a person having a polymorph gene which produced excess PAI-1 would have been successfully treated with an ACE inhibitor because ACE inhibition reduced production of endogenously produced PAI-1.

One of ordinary skill in the art would have been motivated to have used rampril in order to inhibit PAI-1 production, because it is clear that the biochemical mechanism is dependant upon ACE inhibition. Because rampril is a known ACE inhibitor, the ordinary artisan would have had a reasonable expectation that rampril would have acted as a functional equivalent to quinapril to inhibit ACE, especially lacking convincing evidence to the contrary.

Although neither reference specifically taught wherein the patient was a post-menopausal patient, the ordinary artisan would have been motivated to have treated a post-menopausal patient experiencing excess levels of PAI-1 in the blood (caused by

polymorphism of PAI-1 gene) because, as stated *supra,* ACE inhibition reduces production of PAI-1, an underlying causational factor in cardiology related diseases (i.e., thrombosis/myocardial infarction).

Although Brown et al. did not specifically teach wherein the administration of the ACE inhibitor reduced plasma levels of PAI-1 by at least about 35% compared to a baseline, this is considered an intrinsic characteristic of ACE inhibitor administration. The ordinary artisan would have been motivated to vary the amount of ACE inhibitor administered, in order to achieve the most significant decrease in PAI-1 production in order to achieve maximum benefit.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

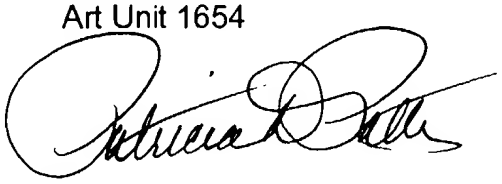
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A Patten whose telephone number is (703) 308-1189. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (703) 306-3220. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-3906.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Patricia A Patten
Examiner
Art Unit 1654

11/20/03



PATRICIA PATTEN
PATENT EXAMINER